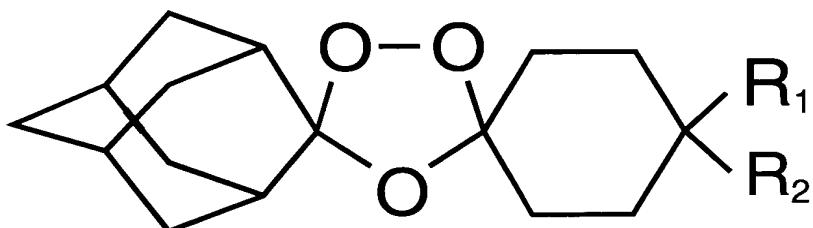


What is claimed is:

1. A spiro or dispiro 1,2,4-trioxolane having the following structure:



5

wherein R<sub>1</sub> and R<sub>2</sub> are the same or different, and are selected from the group consisting of hydrogen, substituted or unsubstituted linear or branched alkyl, aryl, and alkaryl groups and  
10 substituted or unsubstituted alicyclic groups that may be interrupted by one or more oxygen, sulfur or nitrogen atoms, substituted or unsubstituted aromatic or heterocyclic groups that may be interrupted by one or more oxygen, sulfur or nitrogen atoms, a hydroxy group, and a halogen, and further providing that the spirocyclohexyl ring attaching R<sub>1</sub> and R<sub>2</sub> may be interrupted by one or more oxygen, sulfur, or nitrogen atoms.

15

2. The trioxolane of claim 1 whereby R<sub>1</sub> is hydrogen and R<sub>2</sub> is (CH<sub>2</sub>)<sub>n</sub>-Y; whereby Y is a functional group selected from the group consisting of an alkyl, ketone, acid, alcohol, amine, amide, sulfonamide, guanidine, ether, ester, oxime, urea, oxime ether, sulfone, lactone, carbamate, semicarbazone, phenyl, and heterocycle; and n is an integer.

20

3. The trioxolane of claim 1 whereby Y is a non-acidic functional group.

4. The trioxolane of claim 3 whereby Y is a weak base.

25

5. The trioxolane of claim 5 whereby Y is an amide.

6. The trioxolane of claim 2 whereby n = 1.

7. The spiro or dispiro 1,2,4-trioxolane of claim 1 wherein the 1,2,4-trioxolane is selected from the group consisting of: OZ271, OZ277, OZ281, OZ279, OZ288, OZ289, OZ290, OZ296, OZ297, OZ298, OZ301, OZ305, OZ309, OZ315, OZ317, OZ319, OZ320, OZ323, OZ329, OZ333, OZ335, OZ336, OZ337, OZ338, and OZ339.

5

8. The spiro or dispiro 1,2,4-trioxolane of claim 7 wherein the 1,2,4-trioxolane is selected from the group consisting of OZ271, OZ277, OZ279, OZ301, OZ305, OZ315, OZ317, OZ319, OZ323, OZ329, OZ338, and OZ339.

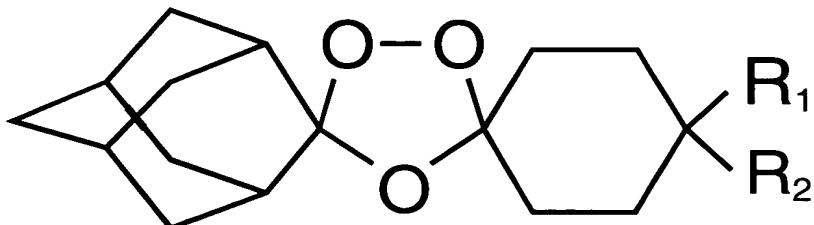
10 9. *Cis*-adamantane-2-spiro-3'-8'-[[[(2'-amino-2'-methylpropyl)amino]carbonyl)methyl]-1',2',4'-trioxaspiro[4.5]decane *p*-tosylate.

10. *Cis*-adamantane-2-spiro-3'-8'-[(1'-piperazinylcarbonyl)methyl]-1',2',4'-trioxaspiro[4.5]decane *p*-tosylate.

15 11. *Cis*-Adamantane-2-spiro-3'-8'-[[[(1'-piperazinylcarbonyl)amino]methyl]-1',2',4'-trioxaspiro[4.5]decane *p*-tosylate.

20 12. *Cis*-Adamantane-2-spiro-3'-8'-[[[(4'-amino-1'-piperidinyl)carbonyl)methyl]-1',2',4'-trioxaspiro[4.5]decane *p*-tosylate.

25 13. A pharmaceutical composition for prophylaxis and treatment of malaria comprising: a malaria prophylaxis or malaria treatment-effective amount of a spiro or dispiro 1,2,4-trioxolane, its prodrugs and optical isomers thereof, and a pharmaceutically acceptable carrier, said trioxolane having the following structure:



wherein R<sub>1</sub> and R<sub>2</sub> are the same or different, and are selected from the group consisting of hydrogen, substituted or unsubstituted linear or branched alkyl, aryl, and alkaryl groups and substituted or unsubstituted alicyclic groups that may be interrupted by one or more oxygen, sulfur or nitrogen atoms, substituted or unsubstituted aromatic or heterocyclic groups that may be interrupted by one or more oxygen, sulfur or nitrogen atoms, a hydroxy group, and a halogen, and further providing that the spirocyclohexyl ring attaching R<sub>1</sub> and R<sub>2</sub> may be interrupted by one or more oxygen, sulfur, or nitrogen atoms.

10 14. The pharmaceutical composition of claim 13 whereby R<sub>1</sub> is hydrogen and R<sub>2</sub> is (CH<sub>2</sub>)<sub>n</sub>-Y; whereby Y is a functional group selected from the group consisting of an alkyl, ketone, acid, alcohol, amine, amide, sulfonamide, guanidine, ether, ester, oxime, urea, oxime ether, sulfone, lactone, carbamate, semicarbazone, phenyl, and heterocycle; and n is an integer.

15 15. The pharmaceutical composition of claim 14 whereby Y is a non-acidic functional group.

16. The pharmaceutical composition of claim 14 whereby Y is a weak base.

20 17. The pharmaceutical composition of claim 16 whereby Y is an amide.

18. The pharmaceutical composition of claim 14 whereby n = 1.

25 19. The pharmaceutical composition of claim 13 wherein the trioxolane is selected from the group consisting of: OZ271, OZ277, OZ281, OZ279, OZ288, OZ289, OZ290, OZ296, OZ297, OZ298, OZ301, OZ305, OZ309, OZ315, OZ317, OZ319, OZ320, OZ323, OZ329, OZ333, OZ335, OZ336, OZ337, OZ338, and OZ339.

20. The pharmaceutical composition of claim 19 wherein the trioxolane is selected from the group consisting of OZ271, OZ277, OZ279, OZ301, OZ305, OZ315, OZ317, OZ319, OZ323, OZ329, OZ338, and OZ339.

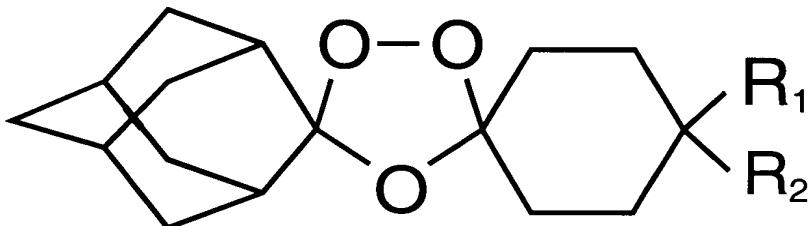
5 21. The pharmaceutical composition of claim 13 wherein the 1,2,4-trioxolane is *cis*-adamantane-2-spiro-3'-8'-[[[(2'-amino-2'-methylpropyl)amino]carbonyl]methyl]-1',2',4'-trioxaspiro[4.5]decane *p*-tosylate.

10 22. The pharmaceutical composition of claim 13 wherein the 1,2,4-trioxolane is *cis*-adamantane-2-spiro-3'-8'-[(1'-piperazinylcarbonyl)methyl]-1',2',4'-trioxaspiro[4.5]decane *p*-tosylate.

15 23. The pharmaceutical composition of claim 13 that is suitable for administration by a method selected from the group consisting of oral, subcutaneous, intravenous, intranasal, rectal, sublingual, and buccal.

24. A method of preventing or treating malaria comprising: administrating a malaria prevention or malaria treatment effective amount of a spiro or dispiro 1,2,4-trioxolane in a pharmaceutically acceptable carrier, said trioxolane having the following structure:

20



wherein R<sub>1</sub> and R<sub>2</sub> are the same or different, and are selected from the group consisting of  
25 hydrogen, substituted or unsubstituted linear or branched alkyl, aryl, and alkaryl groups and substituted or unsubstituted alicyclic groups that may be interrupted by one or more oxygen, sulfur or nitrogen atoms, substituted or unsubstituted aromatic or heterocyclic groups that may be interrupted by one or more oxygen, sulfur or nitrogen atoms, a hydroxy

group, and a halogen, and further providing that the spirocyclohexyl ring attaching R<sub>1</sub> and R<sub>2</sub> may be interrupted by one or more oxygen, sulfur, or nitrogen atoms.

25. The method of claim 24 whereby R<sub>1</sub> is hydrogen and R<sub>2</sub> is (CH<sub>2</sub>)<sub>n</sub>-Y; whereby Y is  
5 a functional group selected from the group consisting of an alkyl, ketone, acid, alcohol,  
amine, amide, sulfonamide, guanidine, ether, ester, oxime, urea, oxime ether, sulfone,  
lactone, carbamate, semicarbazone, phenyl, and heterocycle; and n is an integer.

26. The method of claim 24 wherein the trioxolane is administered in a dose of between  
10 about 0.1-1000 mg/kg/day.

27. The method of claim 26 wherein the trioxolane is administered in a dose of between  
about 1-100 mg/kg/day.

15 28. The method of claim 24 wherein the trioxolane is administered in a single dose.

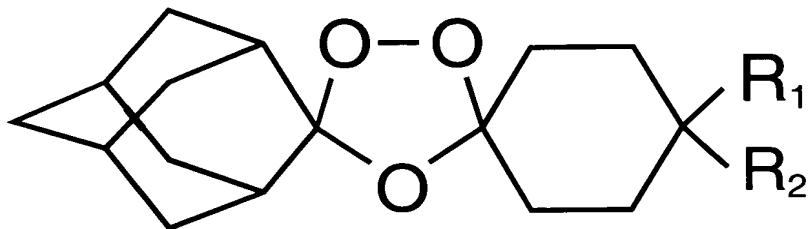
29. The method of claim 24 wherein the trioxolane is administered in divided doses.

30. The method of claim 24 wherein the trioxolane is administered in a malaria-  
20 preventive dose beginning 1-2 weeks prior to malaria exposure and ending 1-2 weeks post  
exposure.

31. A method of claim 24 wherein the trioxolane is administered in a malaria-curative  
dose over 1-10 days.

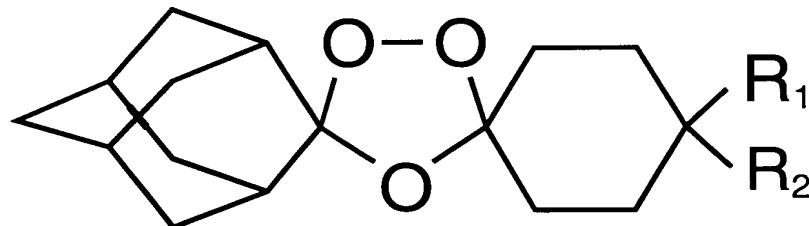
25  
32. A method of manufacturing a composition for prophylaxis and treatment of malaria  
comprising: mixing a malaria prophylaxis or malaria treatment-effective amount of a spiro  
or dispiro 1,2,4-trioxolane, its prodrugs and optical isomers thereof, with a  
pharmaceutically acceptable carrier, said trioxolane having the following structure:

30



wherein R<sub>1</sub> and R<sub>2</sub> are the same or different, and are selected from the group consisting of  
5 hydrogen, substituted or unsubstituted linear or branched alkyl, aryl, and alkaryl groups and  
substituted or unsubstituted alicyclic groups that may be interrupted by one or more  
oxygen, sulfur or nitrogen atoms, substituted or unsubstituted aromatic or heterocyclic  
groups that may be interrupted by one or more oxygen, sulfur or nitrogen atoms, a hydroxy  
group, and a halogen, and further providing that the spirocyclohexyl ring attaching R<sub>1</sub> and  
10 R<sub>2</sub> may be interrupted by one or more oxygen, sulfur, or nitrogen atoms.

33. A method of treating cancer comprising:  
administering a cancer treatment effective amount of a spiro or dispiro 1,2,4-trioxolane in  
15 a pharmaceutically acceptable carrier, said trioxolane having the following structure:

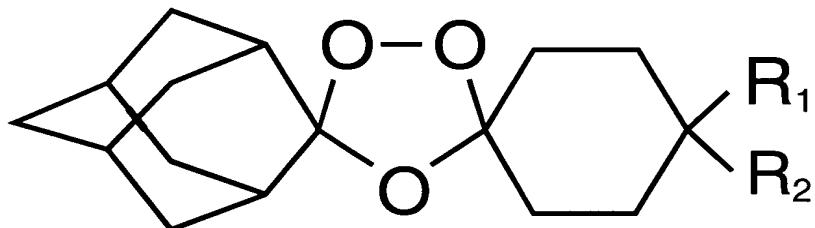


20 wherein R<sub>1</sub> and R<sub>2</sub> are the same or different, and are selected from the group consisting of  
hydrogen, substituted or unsubstituted linear or branched alkyl, aryl, and alkaryl groups and  
substituted or unsubstituted alicyclic groups that may be interrupted by one or more  
oxygen, sulfur or nitrogen atoms, substituted or unsubstituted aromatic or heterocyclic  
groups that may be interrupted by one or more oxygen, sulfur or nitrogen atoms, a hydroxy

group, and a halogen, and further providing that the spirocyclohexyl ring attaching R<sub>1</sub> and R<sub>2</sub> may be interrupted by one or more oxygen, sulfur, or nitrogen atoms.

34. A method of prophylaxis or treatment of schistosomiasis comprising:

5 administrating a schistosomiasis prophylaxis or treatment effective amount of a spiro or dispiro 1,2,4-trioxolane in a pharmaceutically acceptable carrier, said trioxolane having the following structure:



10

wherein R<sub>1</sub> and R<sub>2</sub> are the same or different, and are selected from the group consisting of hydrogen, substituted or unsubstituted linear or branched alkyl, aryl, and alkaryl groups and substituted or unsubstituted alicyclic groups that may be interrupted by one or more

15 oxygen, sulfur or nitrogen atoms, substituted or unsubstituted aromatic or heterocyclic groups that may be interrupted by one or more oxygen, sulfur or nitrogen atoms, a hydroxy group, and a halogen, and further providing that the spirocyclohexyl ring attaching R<sub>1</sub> and R<sub>2</sub> may be interrupted by one or more oxygen, sulfur, or nitrogen atoms.

20 35. A method of synthesizing a dispiro 1,2,4-trioxolane comprising: treating a trioxolane having a functional group selected from the group consisting of a ketone, an aldehyde, an ester, and a phthalimide with a reagent to form a compound selected from the group consisting of lactone, alcohol, oxime ether, hydrazone, ketal, acetal, amine, and acid.

25 36. The method of claim 35 wherein the trioxolane has a ketone or an aldehyde functional group, and is treated with an oxidizing agent to form a lactone or an acid.

37. The method of claim 36 wherein the trioxolane has a ketone or an aldehyde functional group, and is treated with a reducing agent to form an amine or an alcohol.

38. The method of claim 36 wherein the trioxolane has a ketone or an aldehyde functional group, and is treated with a hydroxylamine or a hydrazine to form an oxime ether or a hydrazone, respectively.

39. The method of claim 35 wherein the trioxolane has a ketone or an aldehyde functional group, and is treated with one or more diols and/or alcohols to form a ketal or  
10 acetal.

40. The method of claim 36 whereby the trioxolane is OZ05.

41. The method of claim 40 whereby OZ05 is treated with a heteroaryllithium,  
15 aryllithium, or alkylolithium reagent to form the corresponding tertiary alcohol.

42. The method of claim 37 wherein the trioxolane has an ester functional group, and is treated with a reducing agent to form an alcohol.

20 43. The method of claim 42 whereby the trioxolane is selected from the group consisting of OZ70 and OZ61.

44. The method of claim 43 whereby OZ70 is treated with a reducing agent to form OZ119.

25 45. The method of claim 43 whereby OZ61 is treated with a reducing agent to form OZ89.

46. The method of claim 39 wherein the trioxolane has an ester functional group, and is  
30 treated with a hydrolyzing agent to form an acid.

47. The method of claim 46 wherein the hydrolyzing agent is aqueous potassium hydroxide.

48. The method of claim 46 wherein OZ61 is treated with a hydrolyzing agent to form

5 OZ78.

49. The method of claim 35 wherein the trioxolane has an phthalimide functional group, and is treated with a deprotecting reagent to form an amine.

10 50. The method of claim 49 whereby the phthalimide is selected from the group consisting of OZ136, OZ146, and OZ167.

51. The method of claim 50 whereby OZ136 is treated with a deprotecting reagent to form OZ137.

15

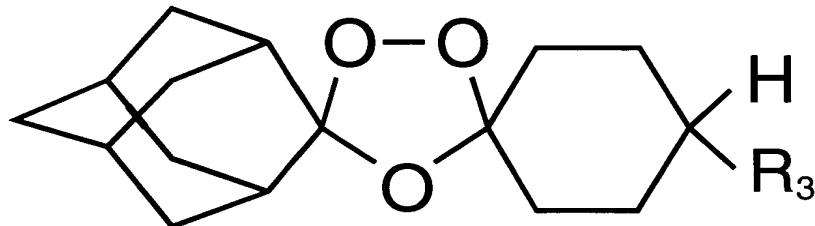
52. The method of claim 50 whereby OZ146 is treated with a deprotecting reagent to form OZ181.

53. The method of claim 52 whereby OZ167 is treated with a deprotecting reagent to  
20 form OZ269.

54. The method of claim 53 wherein the deprotecting reagent is hydrazine.

55. A spiro or dispiro 1,2,4-trioxolane having the following structure:

25



whereby R<sub>3</sub> is (CH<sub>2</sub>)<sub>n</sub>-Y, and further providing that Y is a weak base amide; and n is an integer.

56. The trioxolane of claim 55 whereby n = 1.